REMARKS

Claims 6-8 are pending.

Claim Rejections -- 35 U.S.C. 103

Applicants respectfully traverse the obviousness rejections of claims 6-8 over Chang (Acta Pharmacologica Sinica, August 2003, 24: 796-804) further in view of Lee (US 6,716,822) and Izozumi (Tokai J. Exp. Clin. Med., 1998, vol. 23, pp. 103-117).

The claims are directed to a method of treating cerebral infarct comprising administering a therapeutically effective dose of (s)-3-n-butylphthalide (L-NBP) to reduce the volume of the cerebral infarct. The Examiner relied on Chang for a disclosure of using L-NBP to improve ischemia-induced apoptosis. However, that disclosure of Chang does not lead to the claimed method because Chang's disclosure that L-NBP could improve the apoptosis induced by transient focal cerebral ischemia does not mean that a person of ordinary skill in the art would reasonably expect that L-NBP reduces the volume of the cerebral infarct. An improvement of apoptosis induced by transient focal cerebral infarct does not necessarily mean that the cerebral infarct is treated, let alone that the volume of the cerebral infarct would be reduced. As explained in the Response filed by applicants on December 22, 2009, the relationship of neuronal apoptosis and infarct size is complicated because inhibition of neuronal apoptosis is not always correlated with a reduction in the volume of cerebral infarct. For instance, Wang et al. demonstrated that TACE inhibitor reduced infarct size, but the TACE inhibitor had no effect on apoptosis (Wang et al., *Inhibition of tumor necrosis factor-alpha-converting enzyme by a selective antagonist protects brain from focal ischemic injury in rats,* Mol. Pharmacol. 2004; 65(4):890-6, a copy of which was attached to the Supplemental Response filed on June 29, 2009). With a knowledge of the disclosures of Wang et al., the person of ordinary skill in the art would not automatically equate an improvement in apoptosis with a reduction in the volume of cerebral infarct. Thus, the person would not have reasonably expected that the improvement of apoptosis achieved by L-NBP as disclosed by Chang would result in a reduction in the volume of cerebral infarct.

The secondary references, Lee and Izozumi, do not cure this deficiency of Chang. Lee discloses that antibacterial agents of quinolones, quinones, aminoglycosides or chloramphenicol

inhibit apoptosis in cells exposed to a lack of oxygen, i.e., hypoxia, and a lack of glucose, i.e., hypoglycemia, in cell cultures (column 2, lines 63-67; column 3, lines 8-15). Lee also reported an *in vivo* experiment with rats (column 4, line 56 to column 5, line 38). In the experiment, Lee administered geneticin antibiotic or doxycycline antibiotic in the rats. The rats were anesthetized and then the left anterior descending artery of the heart was ligated to reduce or stop the blood flow to an area of the heart. Two hours after the ligation, the ligature was removed to let the blood flow resume and the heart was excised for determination of cardiac ischemia and cardiac infarct. Lee found that the geneticin or doxycycline treated rats had reduced cardiac ischemia compared with the control rats (the saline-treated rats) in the heart (column 5, lines 17-35). However, it should be noted that the geneticin and doxycycline were administered to the rats BEFORE the induction of cardiac ischemia, so it is not clear whether the geneticin or doxycycline worked to PREVENT the cardiac ischemia, or whether the geneticin or doxycycline would work to TREAT the cardiac ischemia. Secondly, applicants note that Lee did not determine the presence of apoptosis, let alone to quantify the amount of apoptosis, in the heart of these rats, so it is not clear whether the geneticin or doxycycline caused any change in apoptosis in the heart of these rats. Thirdly, even if apoptosis reduction were assumed in the geneticin- or doxycycline-administered rats (the assumption is made for argument purposes only, and should not be construed as acquiescence that Lee showed that geneticin or doxycyline did reduce apoptosis in the heart of the rats with cardiac ischemia), it is also not clear whether the reduction of the infarct area in the geneticin- or doxycycline-treated rats was caused by the assumed apoptosis reduction, or caused by geneticin or doxycycline itself independent of any apoptosis reduction. In addition, Lee's *in vivo* experiment only tried to determine the effects of geneticin and doxycycline on the heart of the rat, and it is not clear whether the effects observed by Lee could be extrapolated into another organ such as the brain with cerebral infarct. In other words, it is not clear whether the *in vivo* findings made by Lee on geneticin and doxycycline concerning cardiac ischemia could be applied to cerebral infarct. Thus, due to these uncertainties, applicants submit that Lee does not cure the deficiency of Chang.

Citing the abstract, the Examiner relied on Lee "as a supplemental reference to demonstrate the state of the art knowledge in using apoptosis-inhibiting agent for the treatment of cerebral infarction" (see Page 3, second to the last paragraph, Office Action). Applicants contend that the reliance of the Examiner on Lee is misplaced. Ostensibly, the Examiner relied

on the part of the abstract of Lee which discloses that antibacterial agents of quinolones, quinones, aminoglycosides or chloramphenicol "can be clinically for ischemic diseases such as applied as a **potential drug** for ischemia-associated infarction and cerebral infarction." (emphasis added). However, the Examiner neglected the fact the quotation reproduced above taken from the abstract of Lee is preceded by the statement that: "Since the invented therapeutic agent improved the viability of cells under hypoxic and hypoglycemic condition." The improvement on the viability of cells under hypoxic and hypoglycemic condition was demonstrated by Lee with antibacterial agents of quinolones, quinones, aminoglycosides or chloramphenicol using *in vitro* cell cultures (column 4, lines 16-54). The *in vitro* cell culture experiments of Lee fail to show that these antibacterial agents would be successful in reducing the volume of cerebral infarct. Furthermore, having a potential as a drug for ischemia-associated infarction and cerebral infarction does not show a reasonable expectation that any of the antibacterial agents would indeed succeed in treating cerebral infarct, let alone reducing the volume of cerebral infarct. Thus, this is another reason that Lee fails to cure the deficiency of Chang.

Izozumi, the other secondary reference, also fails to cure the deficiency of Chang. The Office Action relies on Izozumi as a supplemental reference to demonstrate the state of the art in using the focal cerebral ischemia model as an experimental model of cerebral infarction. Izozumi is silent on the relationship between apoptosis and any reduction in the volume of cerebral infarct.

As a result, there would have been no reasonable expectation based on Chang further in view of Lee and Izozumi that L-NBP would be effective in reducing the volume of the cerebral infarct.

At least based on the above reasons, the obviousness rejections of claims 6-8 over Chang further in view of Lee and Izozumi should be withdrawn.

In the event that the filing of this paper is deemed not timely, applicants petition for an appropriate extension of time. The Office is hereby authorized to charge any fees in relation to this paper under 37 C.F.R. 1.16 and 1.17 to the Kenyon & Kenyon Deposit Account No. 11-0600.

Respectfully submitted,

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